"Version with markings to show changes made." M.P.E.P §714

4. (amended) A method for the prevention of the transfer of plasmid materials containing genes capable of resisting the antibiotic vancomycin from a vancomycin resistant strain of bacteria to another, different strain of bacteria comprising administering to a human or other warm blooded animal harboring bacteria containing said plasmid materials an effective amount of the compound 4,4-methylenebis (tetrahydro-1,2,4-thiadiazine-1,1-dioxide).

6. (amended) The method of claim 4 wherein said 4,4-methylenebis [methylenebix] (tetrahydro-1,2,4-thiadiazine-1, 1-dioxide) is combined with at least one additional antibiotic.

Please note that both a Revocation of Power of Attorney and Power of Attorney were filed with the Office on May 6, 2002, and acknowledged by return postcard stamped May 15, 2002. Those filings indicated that the law office of Carella, Byrne et al. was the new correspondence address for this application. That correspondence address is fully set forth on the last page of this Amendment. Please be sure that all further correspondence is sent to that address.

REMARKS

Reconsideration of the application in view of both the above amendment and the following remarks is requested.

The Office Action rejects claims 4-6 under 35 U.S.C. §102 as being unpatentable over U.S. Patent 6,011,030 issued January 4, 2000 to Pfirrmann—hereinafter "Pfirrmann."

Claim Rejection - 35 U.S.C. §102

None of the claims are anticipated by the Pfirrmann reference. Anticipation under 35 U.S.C. §102 requires that each and every element of the claimed invention be *identically* disclosed in a *single* prior art reference. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988). Additionally, the *single* prior art reference must disclose those elements *as they are arranged in the claim in question.* Lindemann Maschinenfabrik Gmbh v. American Hoist and Derrick Company, 730 F.2d 1452, 1458 (Fed. Cir. 1984). Finally, the single prior art reference is *not* anticipating if it does not disclose an identity of *structure*, *purpose*, and *result* with the claimed invention. Tate Engineering, Inc. v. United States, 477 F.2d 1336, 1342 (Court of Claims 1973).

The instant claims, as most broadly embodied by independent claim 4, are directed to methods that use taurolidine to prevent the transfer of gene-containing plasmid materials from a vancomycin-resistant strain of bacteria to another, different strain of bacteria. Pfirrmann makes no mention of *plasmids* or *genes* or the bacteria-to-bacteria *transfer* of either. Applicants do not dispute the Examiner's position that

Pfirrmann teaches the use of antimicrobial compounds, such as taurolidine, to treat bacterial infections, whereby the impact of endotoxin release is significantly diminished. Indeed, Applicants' *own* disclosure instructs that taurolidine possesses such qualities:

> "**This compound also has the ability to neutralize endotoxin in vitro** and it also exhibits marked anti-adherence properties in vitro. (Specification page 3, lines12-14, emphasis added).
>
> "**The compound demonstrates endotoxin neutralizing activity**, inhibits adherence, is more active at low pH which may prevail at the site of infections or within phagolysosomes, is slightly more active when tested in serum-supplemented media, **and inhibits potential bacterial toxins such as staphylococcal coagulase.**" (Specification page 4, lines 16-20, emphasis added).

Yet, Applicant cannot agree with the Examiner's contention that "[t]he bacterial toxins referred to in the Pfirrmann patent encompass the plasmid materials disclosed in instant Claim 1 [sic Claim 4]." It is well-known in the art, and conceded by Pfirrmann, that an endotoxin is a toxin that is derived from a *disruption* of the outer membrane of Gram-negative bacteria. (Pfirrmann column, 1, lines 33-36). It is equally well-known in the art that an exotoxin is a toxin that is *secreted* by living bacteria. A bacterial plasmid is neither an endotoxin nor an exotoxin, but rather, is a small circular duplex DNA molecule, capable of transferring characteristics such as drug resistance from one bacterial cell to another.

Applicant also disputes the Examiner's position that Pfirrmann's recitation of "a list of bacterial and/or fungal infection," such as *S. aureus* and vancomycin-resistant *E. faecalis*, anticipates the elements of Claims 4 and 5, whereby plasmid materials are prevented from transferring from a vancomycin-resistant strain of bacteria to another, different strain. The citation referred to by the Examiner (column 3, ¶4) indicates that the Pfirrmann invention is "directed to a method of treating a patient with microbial

infection, such as bacterial and/or fungal infection." The paragraph goes on to recite sixteen different strains of microorganism against which the invention is useful for *patient treatment*. Two of the sixteen strains for which Pfirrmann commends taurolidine for treating patients are microorganisms that are already resistant to antibiotics—methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. Pfirrmann does not disclose anything about *preventing* the bacterial *transfer* of drug resistance, in general, nor with regard to vancomycin in particular—this is not Pfirrmann's *purpose*. As explained by his *Abstract*, Pfirrmann's *purpose* is the use antimicrobials, such as taurolidine, *to treat patients with symptoms.* As his *Detailed Description of Preferred Embodiments* further explains:

> "**After identifying a patient exhibiting symptoms** of microbial infection, toxic effects of microbial infection or sepsis, antimicrobial amounts of **Taurolidine and/or Taurultam are administered** intraperitoneally or intravenously to the patient, without and prior to administration of an antibiotic, so as to substantially inactivate microbes and their toxins that are causing the infection." (column 3, lines 27-34, emphasis added).

Clearly, Pfirrmann's *purpose* is to treat symptoms, with the *result* of improving upon a patient's condition. Pfirrmann's focus is indifferent to any predisposition the microorganism causing those symptoms might have toward *any* antibiotic. Indeed, the only Pfirrmann Example to address an *actual* strain of microorganism (Example 3) commends Taurolidine *to treat symptoms* caused by *an already-antibiotic-resistant* strain of *S. aureus*:[1]

> "**The boy was extremely toxic, had generalized <u>myalgia, a stiff neck and pain</u> in the right liliac fossa. The culture finally gave a growth of Staph. aureus resistant to Penicillin, Ampicillin and Amoxycillin.** Intravenous Fucidin was added, but **<u>the boy's condition was getting</u>**

[1] Dependent Claim 5 is specifically directed to using taurolidine to *prevent* Staph. aureus from *acquiring* drug resistance <u>not</u>, as Example 3 directs, *treating symptoms caused by an already resistant* strain of Staph. aureus.

> worse....**An initial dose of 4gms was given intravenously as Taurolin® 2% Solution** via central catheter over four hours, and thereafter 2 gms were given every six hours being infused by drop infusion over a two hour period. **On starting the Taurolin® the temperature immediately fell to 37° C and by the following day the boy had very much improved. Every time the Taurolin® infusion was started the temperature came down and the toxicity disappeared**." (column 3, lines 33-50, emphasis added).

By contrast, the *purpose* of the instant claims is one of *prevention*. Claim 4 does not focus on *symptoms*; it focuses on the infectious microorganism's predisposition toward the particular antibiotic, vancomycin. Unlike Pfirrmann's disclosure, it is an element of the instant claims that the subject (human or other warm-blooded animal) be harboring bacteria that actually contain the gene-carrying plasmids that are capable of transferring vancomycin resistance. The intended *result* of the instant claims is not just the improvement of an isolated patient's condition, but rather, an improvement on the Public Health at large by curtailing the degree to which bacteria can transfer their vancomycin resistance, and thereby, prematurely obsolesce one of the most important antibiotics yet discovered:

> "...a study by the Federal Centers for Disease Control in Atlanta, Georgia, has shown that **nearly eight percent of all enterococci isolated in hospitals nationwide were resistant to vancomycin, the antibiotic considered to be the last line of defense against organisms impervious to other drugs. This was more than 20 times the rate of resistance to vancomycin detected only four years earlier.**" (Specification page 7-8, emphasis added).

Focused on *purposes* and *results* so disparate from those of the instant claims, it is not surprising that Pfirrmann also fails to disclose identical structure. As Applicant's specification instructs:

> **"Resistance to antibiotics is developed in bacterium cells in a small circle of DNA known as plasmid which is matter consisting of a**

> **double-stranded DNA that is apart from the chromosomes but carries genes for a variety of functions and can replicate itself. The genes are concerned with such functions as resistance to antibiotics.** Plasmids are separate from the rest of the bacterium, and they can move quite easily from one bacterium to another. This transferability of plasmids enables resistance genes to spread rapidly even among different species of bacteria. **Transfer between bacteria of plasmids is accomplished through the use of F pili which are fine filaments resembling flagellum which are outgrowths from the bacteria cells which normally function to propel the cell, however when the F pili attach to another cell, a bridge is formed which permits the plasmids to spread rapidly from one cell to another.**" (Specification page 8, emphasis added).

Pfirrmann discloses nothing about the structural claim elements that relate to preventing the bacteria-to-bacteria transfer of vancomycin resistance such as *capable genes*, *plasmid materials*, or the *host's harboring of bacteria that contain such materials*. To the extent Pfirrmann does not *identically* disclose each and every element *as they are arranged* by the instant claims, and to such further extent fails to disclose their identical *structure*, *purpose*, and *result*, Pfirrmann fails to anticipate the instant claims.

In view of the foregoing, Applicant submits that claims 4-6 are not anticipated by the Pfirrmann reference. As the instant application appears to be in condition for allowance, Applicant requests its prompt passage to issue.

It is believed that no fee is due. However, if any fee is due it should be charged to Deposit Account No.: 03-0678.

CERTIFICATE OF MAILING

Deposit Date: December 4, 2002

I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service with sufficient postage as First Class Mail to Addressee, under 37 CFR 1.8, on the date indicated above addressed to:

**Commissioner of Patents and Trademarks
Washington, DC 20231**

12/4/02

Raymond E. Stauffer, Esq. **Date**

#161568 v1 - response to office action

Respectfully submitted,

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